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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/607,974	06/30/2003	Ginette Serrero	27600-00014-US1	6971

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EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/607,974	SERRERO, GINETTE	
	Examiner	Art Unit	
	TERRA C. GIBBS	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-37,39 and 40* is/are pending in the application.

4a) Of the above claim(s) *40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-37 and 39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission mailed on March 31, 2008 has been entered.

Claims 28, 30, 31, and 33-35 have been amended.

Claims 28-37, 39, and 40 are pending in the instant application.

Claim 40 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on May 11, 2007.

Accordingly, claims 28-37 and 39 have been examined on the merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments

Applicant's Amendment and Response filed May 11, 2007 have been considered. Rejections and/or objections not reiterated from the previous Office Action mailed October 31, 2007 are hereby withdrawn. Any arguments addressing said rejections and/or objections are moot. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections

presently applied to the instant application.

Double Patenting

In the previous Office Action mailed August 15, 2006, claims 28-37 were rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 5-7 and 10 of U.S. Patent No. 6,670,183 ('183). **This rejection is maintained** for the reasons of record set forth in the previous Office Action mailed August 15, 2006.

Response to Arguments

In response to this rejection, Applicants request that this rejection be held in abeyance until the claims are otherwise in a condition for allowance. This request has been considered and it is noted that that this rejection will be held in abeyance until the claims are otherwise in condition for allowance.

Claim Rejections - 35 USC § 112

In the previous Office Action mailed October 31, 2007, claims 28-37 and 39 were rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting the growth of a tumor cell or a method of inhibiting the protein expression of 88kDa glycoprotein growth factor (GP88) in a cell, comprising the subcutaneous injection of a GP88 antisense oligonucleotide targeted to SEQ ID NO:16, using primer pairs SEQ ID NO:12 and SEQ ID NO:14, wherein said antisense

inhibits the growth of the tumor cell or inhibits the protein expression of GP88, does not reasonably provide enablement for a method of inhibiting the growth of a tumor cell or a method of inhibiting the protein expression of GP88 in a cell, comprising any route of administration of any antisense targeted to GP88, wherein said antisense inhibits the growth of the tumor cell or inhibits the protein expression of GP88. **This rejection is maintained** for the reasons of record set forth in the previous Office Action mailed October 31, 2007.

Response to Arguments

In response to this rejection Applicants argue that the specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Applicants point the examiner to the MPEP 8th Edition Revision 6 at § 2164.04. This argument has been considered, but is not found persuasive because in view of the weighing of the *Wands Factors* and the many discussions regarding the unpredictability of using antisense oligonucleotides *in vivo*, said discussions made of record in the previous Office Actions mailed August 15, 2006 and February 3, 2006, it is the Examiner's firm position that one of ordinary skill in the art would have to perform undue experimentation to practice the invention over the scope claimed. Thus, the *Wands*

Factors have been weighed and favor and support undue experimentation.

Applicants also argue that the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. Applicants point the examiner to the MPEP 8th Edition Revision 6 at § 2164.01. This argument has been fully considered, but is not found persuasive because the *Wands Factors* have been weighed and they do not favor complex experimentation. Instead, the *Wands factors* have been weighted and favor undue experimentation, given the broad claims in an art whose nature is identified as unpredictable, the state of the prior art, the lack of guidance in the specification, the breadth of the claims, and the quantity of experimentation necessary to practice the claimed invention.

Applicants argue that compliance with the enablement requirement does not turn on whether an example is disclosed. This argument has been fully considered, but is not found persuasive because working examples are, of course, not an absolute requirement for enablement, but are a legitimate factor in determining lack of enablement, especially when the art is of an unpredictable nature. See *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). As discussed *supra*, the *Wands factors* have been weighted and favor and support undue experimentation.

Applicants argue that the specification need not contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art would be able to practice the invention without an undue amount of experimentation. This argument has been fully considered, but is not found persuasive because as discussed *supra*, working examples are, of course, not an absolute requirement for enablement,

but are a legitimate factor in determining lack of enablement, especially when the art is of an unpredictable nature. See *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). The need for additional experimentation, as in routine experimentation, is not an absolute bar to enablement, as long as the required experimentation is not undue. However, the *Wands factors* have been weighed and favor undue experimentation because of the lack of predictability of the art, and the specification lack of particular guidance or particular direction, undue experimentation would be required of one of skill in the art to make and use the claimed invention commensurate in scope with the claims. Further, given the unpredictability in the art of using antisense nucleic acids *in vivo*, it would require more than routine experimentation to make and use the claimed invention. Individually, Branch, Jen et al. Agrawal et al., and Patil et al. (found in the previous Office Actions mailed August 15, 2006 and February 3, 2006) detail the capacity to inhibit gene expression *in vivo* using antisense oligonucleotides as unpredictable, requires trial and error experimentation, and is not a matter of routine screening. Therefore, undue experimentation would be required of one of skill in the art to make and use the claimed invention commensurate in scope with the claims.

Applicants next argue that the claims have been amended to recite that the antisense oligonucleotide is targeted to at least a portion of SEQ ID NO:16 around the translation initiation site and this limitation directs those skilled in the art to specific oligonucleotides that will accomplish the claimed functionality recited in the instant claims. Applicants also argue that based on teachings in the art, those skilled in the art would objectively believe that antisense oligonucleotides targeted to at least a portion of

SEQ ID NO:16 around the translation initiation site would display the claimed functionality. Applicants point the Examiner to Brysch et al., made of record as reference CJJ on Applicant's IDS filed August 14, 2003.

These arguments have been fully considered, but are not found persuasive because although the claims have been amended to recite that the antisense oligonucleotide is targeted to at least a portion of SEQ ID NO:16 around the translation initiation site, contrary to Applicant's assertions, this limitation does not lend any information towards determining those antisense oligonucleotides which carry out the functionality of the instant claims. For instance, Agrawal et al. (Molecular Medicine 2000, made of record on the Office Action mailed February 3, 2006), teach "[O]ur experience, however shows that it is difficult to find a 20-nucleotide site that includes the initiation codon and satisfies all the criteria discussed in this review for optimal antisense oligonucleotide design" (see page 77, first column). Agrawal et al. also teach that "[C]aution must be exerted in experimental design and interpretation of antisense results until all the critical aspects of antisense oligonucleotides are explored beyond reasonable doubt" (see page 80, first column, last paragraph). Therefore, it is quite clear from Agrawal et al. that the activity of an antisense oligonucleotide, including one targeted at or around the translation initiation site, is influenced by its base composition and by its sequence.

Applicants next argue that with regard to the route of delivery, those skilled in the art understand that delivery of antisense oligonucleotides *in vivo* would not require undue experimentation. Applicants point the Examiner to Wang et al. and Mercola et al.

This argument has been fully considered, but is not found persuasive because it should be noted that the claims are so broad to include, for example, systemic delivery. While Wang et al. teach, "[T]hese data quickly led to the conclusion that delivery is not a problem in the application of ODNs [oligonucleotides] *in vivo*", Wang et al. also teach, "[T]hese problems indicate that the *in vivo* application of systemically administered PS-ODNs in simple saline solution may be very limited. New strategies are needed to maximize the clinical activity of ODN therapeutics" (see page 170, left column). Wang et al. also teach that, "[A]n appropriate formulation/delivery method is critical for the successful application of antisense ODNs in cancer therapy" (see page 177, right column). Wang et al. also teach, "[M]any groups have reported exciting *in vitro* results aimed at improving tumor delivery. Unfortunately, few of these results have been successfully translated into animal models" (see page 179, first paragraph, left column). The evidence of record coupled with the teachings of Wang et al., clearly demonstrate that those skilled in the art would understand that delivery of antisense oligonucleotides *in vivo* is unpredictable and is not a matter of routine experimentation.

Furthermore, regarding the fact that the claims are so broad to include systemic delivery, as discussed in the previous Office Action mailed February 3, 2006, Nielsen, PE (submitted and made of record in the Office Action mailed February 3, 2006) reviews the problems associated with nucleic acid-based therapeutics and systemic delivery. Nielsen, PE teach, "Many 'solutions' to this problem have been published on the subject during the last decade, but we yet have to see an effective delivery technology" (see page 956, second paragraph). Nielsen, PE also discuss that a major

unmet challenge for the field is to develop methods that allow effective and simple cellular and especially systemic delivery of antisense agents. Nielsen, PE conclude by discussing the eager anticipation of both academic researchers and the pharmaceutical industry for delivery methods for gene therapy drugs.

Thus, the evidence of record supports that in order to practice the full scope of the invention, more than routine experimentation would be required. In fact, the *Wands Factors* have been weighed and favor undue experimentation. Therefore, the claims remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached on 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information

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tcg
April 9, 2008

/Terra Cotta Gibbs/